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Original Contribution

Reproductive Factors, Exogenous Hormones, and Pancreatic Cancer Risk in the CTS

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Female steroid hormones are hypothesized to play a protective role in pancreatic cancer risk. However, results from epidemiologic studies that examined hormone-related exposures have been inconsistent. The California Teachers Study is a cohort study of female public school professionals that was established in 1995–1996. Of the 118,164 eligible study participants, 323 women were diagnosed with incident invasive pancreatic cancer through December 31, 2009. Multivariable Cox proportional hazards regression methods were used to estimate hazard ratios and 95% confidence intervals for the association of pancreatic cancer risk with reproductive factors and exogenous hormone use. Current users of estrogen-only therapy at baseline (1995–1996) had a lower risk of pancreatic cancer than did participants who had never used hormone therapy (hazard ratio = 0.59, 95% confidence interval: 0.42, 0.84). Use of estrogen-plus-progestin therapy was not associated with the risk of pancreatic cancer. A longer duration of oral contraceptive use (≥10 years of use compared with never use) was associated with an increased risk of cancer (hazard ratio = 1.72, 95% confidence interval: 1.19, 2.49). Reproductive factors, including age at menarche, parity, breastfeeding, and age at menopause, were not associated with pancreatic cancer risk. Our results suggest that increased estrogen exposure through estrogen-only therapy may reduce pancreatic cancer risk in women.

hormone therapy; oral contraceptives; pancreatic cancer

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; CTS, California Teachers Study; EPT, estrogen-plus-progestin therapy; ET, estrogen-only therapy; HR, hazard ratio; HT, hormone therapy; OC, oral contraceptive.

Approximately 30,000 incident cases of invasive pancreatic cancer are diagnosed each year in the United States (1). Fewer than 5% of these patients survive more than 5 years after diagnosis (2–4), and the median survival time ranges from less than 6 months to 17 months depending on stage at diagnosis (5–7). Identification of environmental and lifestyle risk factors for pancreatic cancer will provide insight into the causes of this disease and may suggest subgroups for whom additional medical surveillance is appropriate. Cigarette smoking, which is estimated to explain approximately 15% of pancreatic cancer incidence in the United States (8), is one of the few modifiable lifestyle risk factors for pancreatic cancer (8–12). Obesity has been implicated as another modifiable risk factor (13–16). Type 2 diabetes mellitus is an important pancreatic cancer risk factor (17), and it may at least partially explain the obesity and pancreatic cancer association (13).

Existing evidence has led investigators to hypothesize that female sex steroid hormones may play a protective role in pancreatic cancer risk. Pancreatic cancer is less common in women than in men, with a female-to-male ratio of age-adjusted incidence rates of 0.75 (18). In addition, estrogen has been shown to inhibit the growth of preneoplastic pancreatic lesions or transplanted pancreatic carcinoma in rat models (19, 20). Sex-steroid biosynthetic enzymes and steroid hormone receptors have been detected in both normal and neoplastic human pancreas tissue (21–25).

Epidemiologic studies, particularly case-control studies, examining the associations between pancreatic cancer risk

and reproductive and hormone-related factors in women have generated inconsistent results (26–48). Given the extremely short median survival time of pancreatic cancer patients (4), possible survival bias in case-control studies is a concern. Further, in case-control studies, the use of proxy-interviews for cases who were either very ill or deceased may contribute to differential misclassification of exposures. Although cohort studies have more consistently reported null associations between pancreatic cancer and age at menarche, age at first birth, oral contraceptive (OC) use and hormone therapy (HT) use, findings for parity, breastfeeding, and age at menopause have been inconsistent (27–31, 41, 42). The California Teachers Study (CTS) is a prospective cohort study of women who provided information on reproductive, hormone-related, and lifestyle factors at the time of cohort enrollment. Only a small proportion (≈5%) of CTS participants was currently smoking at enrollment, providing a unique population in which to evaluate other risk factors for pancreatic cancer.

MATERIALS AND METHODS

Participants

The CTS is a prospective cohort study of 133,479 current and former female public school professionals (teachers, nurses, psychologists, and administrators) who were members of the California State Teachers Retirement System in 1995. At baseline, cohort participants completed a mailed questionnaire to provide detailed information on reproductive history, OC and HT use, and personal medical history, including any previous diagnosis of pancreatic or other cancer. The third CTS questionnaire, sent in 2000, was used to obtain updated information on menopausal status and HT use. The design and study methods of the CTS have been described in detail elsewhere (49). The CTS was approved by the institutional review board at each collaborating institution. For the current analysis, the authors excluded, in sequence, cohort participants who at baseline lived outside of California ($n = 8,867$), had an unknown history of cancer ($n = 662$), limited their participation to breast cancer research ($n = 18$), had a prior history of pancreatic cancer ($n = 10$), or were 80 years of age or older ($n = 5,758$). The resulting cohort for this analysis consisted of 118,164 participants.

Case ascertainment and follow-up

Incident invasive pancreatic cancer diagnoses were identified through annual linkages with the California Cancer Registry, which is comprised of 3 Surveillance Epidemiology and End Results registries. There were 323 eligible participants diagnosed with invasive pancreatic cancer (*International Classification of Disease Oncology, Third Edition* site codes C25.0–C25.9) after completing the baseline questionnaire and on or before December 31, 2009. Participants were followed from the date of baseline questionnaire completion until the first of the following events: diagnosis with invasive pancreatic cancer, a move outside of California for more than 4 months ($n = 10,929$), death ($n = 10,467$), or end of follow-up on December 31, 2009 ($n = 96,445$).

Exposure assessment

Determination of menopausal status at baseline was based on answers to questions regarding the timing of and reason for the permanent cessation of menstrual periods, in addition to the timing and type of any relevant gynecologic surgery. Participants who reported ongoing menstrual periods and who had never used hormones for menopausal symptoms were classified as premenopausal. Participants were classified as perimenopausal if they reported that their periods had stopped within the last 6 months and they were not currently pregnant. Participants were classified as postmenopausal if they met any of the following criteria: 1) their periods had stopped more than 6 months before completing the baseline questionnaire, 2) they had undergone a bilateral oophorectomy, 3) they were 56 years of age or older at baseline and not already classified as premenopausal or perimenopausal, or 4) they began using HT before the cessation of their periods. Women who reported a hysterectomy (without bilateral oophorectomy) before 56 years of age and were less than 56 years of age at baseline were considered to be of unknown menopausal status and were excluded from the relevant analyses. The age criterion was based on previous work that indicated that among those who underwent natural menopause, more than 97% were postmenopausal by the age of 56 years (50, 51). For CTS, age at menopause was ascertained in categories (<35, 35–39, 40–43, 44–46, 47–49, 50–52, 53–55, or ≥56 years). Therefore, it was not possible to examine distribution of age in years at natural menopause. Nonetheless, our data suggested that 93% of never-smokers and 93% of former smokers reported an age at natural menopause of 53–55 years or younger, supporting our use of 56 years of age as a cutoff to consider women with unknown menopausal status as postmenopausal. A similar but slightly higher proportion (95%) was observed for current smokers. When we repeated the analysis using 54 years of age as the cutoff for current smokers (56 years of age for never-smokers and former smokers), the results were identical to those presented. We also repeated the analyses after excluding women who began using HT before cessation of their periods, and the results did not differ from those presented. For analytic purposes, the small number of perimenopausal participants ($n = 2,523$) were included in the postmenopausal category, except in the analyses of age at menopause; exclusion of perimenopausal participants did not significantly alter results from those shown.

We classified OC use by using calendar year of use as a proxy for OC formulations (high-dose versus low-dose OCs). Participants who stopped using OCs before 1974 were classified as users of high-dose OC formulations, and those who started using OCs after 1975 were classified as users of low-dose OC formulations because low-dose OC formulations, which contain less than 50 μg of estrogen, were introduced in 1973. The other OC users (i.e., who used OCs before 1973 but stopped using OCs in 1974 or later or who started using OCs in 1975) may have been exposed to both high- and low-dose OCs and were not included in analyses specifically evaluating high- or low-dose OC use. The reference group in all OC analyses was never users of OCs. Prior studies have made similar assumptions regarding year of use and OC dose (52–54).

Table 1. Distribution of Baseline Characteristics Among 118,164 Participants Included in the Present Analysis, the California Teachers Study, 1995–1996[a]

Baseline Characteristics	No.	%
Age at cohort enrollment, years		
22–39	21,237	18.0
40–49	32,363	27.4
50–59	30,207	25.6
60–69	20,681	17.5
70–79	13,676	11.6
Age at menarche, years[b]		
≤11	26,597	22.8
12	32,016	27.5
13	34,326	29.4
≥14	23,613	20.3
OC use		
Never used	35,596	31.3
Former user at baseline	6,659	5.9
Current user at baseline	71,220	62.6
Ever used, unknown if current or former	256	0.2
Duration of OC use, years[c]		
<1	8,947	11.8
1–4	26,355	34.7
5–9	24,076	31.7
≥10	16,488	21.7
Parity		
Nulligravid	23,906	20.6
Gravid, nulliparous	7,124	6.1
1–2 full-term pregnancies	56,306	48.5
≥3 full-term pregnancies	28,721	24.7
Age at first full-term pregnancy, years[d]		
≤19	4,479	5.3
20–24	26,629	31.3
25–29	34,541	40.6
30–34	14,782	17.4
≥35	4,595	5.4
Breastfeeding history[e]		
Never breastfed	19,009	22.5
Ever breastfed	65,796	77.5
Menopausal status/HT use		
Premenopausal	47,993	43.5
Postmenopausal, never used HT	13,956	12.7
Postmenopausal, ever used HT[f]	46,922	43.1
HT use[f,g]		
Past HT user	8,803	19.7
Current user of ET	15,508	34.7
Current user of EPT	20,334	45.5
Age at menopause, years[h]		
≤46	13,067	28.2
47–49	9,083	19.6
50–52	12,666	27.3
≥53	11,571	24.9
Body mass index[i]		
<25	69,318	60.8
25 to <30	28,388	24.9
≥30	16,221	14.2
Smoking history		
Never	77,619	65.7
Former	33,779	28.6
Current	6,084	5.2
History of diabetes	3,298	2.8

Abbreviations: EPT, estrogen-plus-progestin therapy; ET, estrogen-only therapy; HT, hormone therapy; OC, oral contraceptive.

[a] Numbers shown do not include subjects with missing information on pregnancy history ($n = 2,107$), body mass index ($n = 4,237$), smoking status ($n = 682$), age at menarche ($n = 1,558$), OC use ($n = 4,433$), duration of OC use ($n = 6,702$), age at first full-term pregnancy ($n = 1$), breastfeeding ($n = 1$), menopausal status/HT use ($n = 9,293$), age at menopause ($n = 18,886$), and HT use ($n = 1,297$).

[b] Fifty-four participants who had never had a first menstrual period are not shown.

[c] Among OC users.

[d] Among parous participants.

[e] Among participants who ever had a live birth ($n = 84,807$).

[f] Excludes participants who used a progestin-only therapy ($n = 980$).

[g] Among ever HT users.

[h] Among postmenopausal participants.

[i] Weight (kg)/height $(m)^2$.

Table continues

Statistical analyses

Multivariable Cox proportional hazards regression methods were used to estimate hazard ratios and 95% confidence intervals for the associations between hormone-related factors and invasive pancreatic cancer risk, using age in days as the time metric. Models were stratified by age at baseline (in single years of age) and adjusted for race/ethnicity (non-Hispanic white, black, or other; the predominant groups in the "other" category were Hispanic and Asian), body mass index measured as weight in kilograms divided by height in meters squared (<25, 25 to <30, ≥30, or unknown), baseline smoking status (never, former, current, or unknown), self-reported history of diabetes (no or yes), menopausal status (premenopausal, postmenopausal, or unknown), age at menarche (≤11, 12, 13, or ≥14 years or unknown), pregnancy history (nulligravid, gravid nulliparous, 1–2 full-term pregnancies, ≥3

Table 2. Hazard Ratios and 95% Confidence Intervals for the Associations of Reproductive Factors and Exogenous Hormone Use With Pancreatic Cancer Risk Among 118,164 Participants in the California Teachers Study, 1995–2009

	No. of Cases	Person-years	Multivariable HR[a]	95% CI
		All Participants		
Total	323	1,505,060		
Age at menarche, years				
≤11	68	339,542	1.00	Referent
12	82	408,821	0.98	0.71, 1.35
13	84	437,735	0.92	0.66, 1.26
≥14	82	299,088	1.22	0.88, 1.69
P for trend			0.31	
Duration of OC use, years				
Never	156	437,932	1.00	Referent
<1	17	115,325	1.10	0.65, 1.85
1–4	43	342,562	1.15	0.78, 1.68
5–9	36	312,200	1.12	0.74, 1.69
≥10	47	213,768	1.72	1.19, 2.49
P for trend			0.014[b]	
Parity/No. of full-term pregnancies				
Nulligravid	49	302,273	1.00	Referent
Gravid, nulliparous	16	90,651	1.44	0.82, 2.55
1	44	230,145	1.13	0.75, 1.70
2	101	492,786	1.10	0.78, 1.55
3	62	239,027	0.98	0.67, 1.43
≥4	41	124,123	0.94	0.62, 1.44
P for trend			0.68	
Number of full-term pregnancies among parous women				
1	44	230,145	1.00	Referent
2	101	492,786	0.98	0.69, 1.41
3	62	239,027	0.88	0.60, 1.30
≥4	41	124,123	0.83	0.55, 1.29
P for trend			0.31	
Age at first full-term pregnancy among parous women, years				
<22	34	155,583	1.00	Referent
22–24	66	236,863	1.13	0.75, 1.72
25–29	101	442,541	1.12	0.76, 1.67
≥30	47	251,080	1.09	0.69, 1.74
P for trend			0.76	
Breastfeeding[c]				
Never breastfed	73	237,291	1.00	Referent
Ever	175	846,062	1.07	0.81, 1.41

Table continues

full-term pregnancies, or unknown) and HT use at baseline (never, estrogen-only therapy (ET), estrogen-plus-progestin therapy (EPT), both ET and EPT, progestin-only therapy, or unknown) (17). For each covariate, women with missing data were included in the model as a separate category ("unknown"); exclusion of women in the "unknown" category did not appreciably change the results. Using different cutpoints for age at menarche (<13 or ≥13 years; <14 or ≥14 years) or different

Table 2. Continued

	No. of Cases	Person-years	Multivariable HR[a]	95% CI
Menopausal status/HT use at baseline[d]				
Premenopausal	29	631,941	1.00	Referent
Postmenopausal, never used HT	87	169,758	1.31	0.67, 2.59
Postmenopausal, ever used HT	176	574,109	0.93	0.48, 1.78
		Postmenopausal Participants Only		
HT use at baseline[d]				
Never HT user	87	169,758	1.00	Referent
Ever HT user	176	574,109	0.70	0.54, 0.91
HT formulation at baseline[d]				
Never HT user	87	169,758	1.00	Referent
Ever HT user				
Used ET only	74	215,100	0.64	0.47, 0.88
Used EPT only	68	260,774	0.81	0.58, 1.14
Used both ET and EPT	36	107,621	0.72	0.49, 1.06
Recency of use at baseline[d]				
Never HT user	87	169,758	1.00	Referent
Former HT user	43	105,054	0.70	0.48, 1.01
Current ET user	52	192,503	0.59	0.42, 0.84
Current EPT user	75	260,794	0.84	0.61, 1.17
Recency of use at baseline; follow-up truncated at June 30, 2002[d]				
Never HT user	31	86,296	1.00	Referent
Former HT user	13	53,956	0.58	0.30, 1.10
Current ET user	19	96,561	0.66	0.37, 1.17
Current EPT user	24	128,057	1.00	0.57, 1.77
Age at menopause, years				
<47	52	161,767	1.00	Referent
47–49	52	113,213	1.29	0.88, 1.90
50–52	51	157,396	0.79	0.53, 1.17
≥53	65	141,484	0.98	0.68, 1.43

Abbreviations: CI, confidence interval; EPT, estrogen-plus-progestin therapy; ET, estrogen-only therapy; HR, hazard ratio; HT, hormone therapy; OC, oral contraceptive.

[a] All models were stratified by age at baseline (in single years) and adjusted for race/ethnicity (non-Hispanic white, black, or other), body mass index, measured as weight in kilograms divided by height in meters squared (<25, 25 to <30, ≥30, or unknown), menopausal status (premenopausal, postmenopausal, or unknown), HT use (never, ET only, EPT only, both ET and EPT, progestin-only therapy, or unknown), age at menarche (<14 years, ≥14 years, or unknown), total number of full-term pregnancies (nulligravid, gravid nulliparous, 1–2 full-term pregnancies, ≥3 full-term pregnancies, or unknown), smoking status (never, former, current, or unknown), and history of diabetes (no or yes).

[b] Includes participants who never used OCs.

[c] Among participants who ever had a live birth ($n = 84,807$).

[d] Excludes participants who used a progestin-only therapy ($n = 1,116$).

categories of baseline HT use (never user of HT, former HT user, current ET user, current EPT user) as covariates in the models did not change the risk estimates, and neither did adjustment for accumulated pack-years of smoking at baseline. For ordinal variables, linear trend in the natural logarithm of hazard ratios was evaluated across exposure categories using Wald tests. All P values reported are 2-sided. The proportional hazards assumption was tested by examining scaled Schoenfeld residuals (55); no evidence of a violation of the proportional hazards assumption was observed.

To assess whether the changes in the status of HT use over time influenced the hazard ratio estimates, we performed an analysis in which we treated HT use as a time-dependent variable, using information from the baseline questionnaire and the 2000 questionnaire. Baseline values were used until the 2000 questionnaire was completed, at which point those values were used. If no 2000 questionnaire value was available, the baseline value was retained. The proportion of HT users in the CTS dropped significantly during follow-up, from 60% at baseline to 21% in 2005–2006 (56). This is consistent with the national trend in HT use after the publication of the Women's Health Initiative clinical trials (57, 58). Therefore, we performed a sensitivity analysis in which follow-up was limited to the period from baseline through June 30, 2002.

We repeated all analyses excluding 12,039 women who had a history of any type of cancer at baseline based on women's self-report at baseline and the linkage between the cohort and the California Cancer Registry (including diagnoses since 1988), the Los Angeles County Cancer Surveillance Program (including diagnoses since 1972), and the San Francisco-Oakland Surveillance, Epidemiology, and End Results Program (including diagnoses since 1973). Because the results were similar, we present the results or models that excluded only those women with a prior history of pancreatic cancer ($n = 10$).

RESULTS

Baseline characteristics of the eligible analytic cohort are presented in Table 1. Mean age at baseline was 51.9 (standard deviation, 13.2) years. Twenty-one percent of participants had never been pregnant; approximately half (49%) of participants had 1 or 2 full-term pregnancies, and nearly 25% had 3 or more full-term pregnancies. Approximately 60% of the participants were postmenopausal. Among postmenopausal women, 77% had ever used HT, and 80% of them were current users.

OC use and ET use, but not any of the other reproductive and menstrual factors examined, were associated with incidence of pancreatic cancer (Table 2). Participants who used OCs for 10 or more years had a 72% greater risk of pancreatic cancer than did participants who had never used OCs (hazard ratio (HR) = 1.72, 95% confidence interval (CI): 1.19, 2.49). Circulating estrogen levels decrease during the menopausal transition (59, 60), and some perimenopausal women use OCs to control menstrual problems and perimenopausal symptoms (61). To exclude the possibility that the increased risk associated with long-term OC use was due to perimenopausal OC use, we repeated the analyses after excluding participants who used OCs after age 45 years. The hazard ratio associated with OC use for 10 or more years compared with never use was slightly higher (HR = 1.99, 95% CI: 1.23, 3.22). When examined by calendar year of use as a proxy for high-dose versus low-dose OCs, a duration response was present for high-dose OC use (P for trend = 0.027; Appendix Table 1). Participants who used high-dose OCs for 10 or more years had a risk of pancreatic cancer that was more than 2 times greater than that in women who had never used OCs (HR = 2.08, 95% CI: 1.05, 4.12). However, the number of pancreatic cancer diagnoses included in this comparison was limited.

Among postmenopausal participants, both ever use of ET (but not EPT) at baseline (HR = 0.64, 95% CI: 0.47, 0.88; Table 2) and current use of ET at baseline (HR = 0.59; 95% CI: 0.42, 0.84) were statistically significantly associated with a decreased risk of pancreatic cancer. The association between ET use and pancreatic cancer risk did not differ by type of menopause (natural menopause vs. surgical menopause; data not shown). The results did not change when we included HT use as a time-dependent variable; the hazard ratio for current ET use was 0.59 (95% CI: 0.42, 0.85). Upon truncation of follow-up at June 30, 2002, the relative risks associated with current ET use at baseline did not differ markedly from those presented for the full follow-up period (Table 2). However, the relative risks associated with current use of EPT at baseline changed from 0.84 (95% CI: 0.61, 1.17) to 1.00 (95% CI: 0.57, 1.77) when we limited follow-up to June 30, 2002. No duration-of-use effects were observed for ET use or EPT use, but the sample size for these analyses was limited (Table 3).

We conducted an additional analysis of full-term pregnancies that was restricted to postmenopausal participants to address concerns that baseline parity information would not be accurate for women who had not completed their reproductive years; the results did not differ from those presented. Results for age at menopause were similar when the analyses were restricted to postmenopausal participants who had never used HT (data not shown) and when we excluded participants who experienced menopause before 40 years of age (8 pancreatic cancer cases and 3,102 noncases; data not shown). In addition, adjustment for OC use did not appreciably change the hazard ratios for any of the variables presented in Table 2.

After restricting analyses to never-smokers, we observed results similar to those presented for all participants (data not shown), with the exception that the estimated hazard ratios for long-term OC use were larger; the hazard ratios among never-smokers for 5–9 years and ≥10 years of OC use were 1.67 (95% CI: 0.96, 2.89) and 2.47 (95% CI: 1.49, 4.09), respectively. We did not observe evidence that these associations were modified by body mass index.

DISCUSSION

Among the factors examined, only ET use was associated with a lower risk of developing pancreatic cancer. EPT use was not significantly associated with pancreatic cancer risk, particularly after truncating the follow up at 2002, but the 95% confidence intervals substantially overlapped with those for the association with ET use. Long-term OC use was associated with a higher risk of pancreatic cancer. Reproductive and menstrual factors were not associated with pancreatic cancer risk.

Our results suggest that postmenopausal ET use but not EPT use may decrease the risk of pancreatic cancer. Results from previous epidemiologic studies addressing the possible association between HT use and pancreatic cancer risk have been inconsistent (28–31, 34, 38, 45–47, 62), perhaps because of limitations such as information bias and survival bias for case-control studies (34, 38, 45–47, 62), lack of

Table 3. Hazard Ratios and 95% Confidence Intervals for the Association Between Pancreatic Cancer Risk and Duration of Estrogen-only Therapy Use or Estrogen-Plus-Progestin Therapy Use Compared With Never Use of Hormone Therapy in Postmenopausal Participants in the California Teachers Study, 1995–2009[a]

Duration of ET or EPT Use	No. of Cases	Person-years	Multivariable HR[b]	95% CI
Never use of HT	87	169,758	1	Referent
Current ET use at baseline				
Used for <20 years	29	138,356	0.55	0.36, 0.85
Used for ≥20 years	19	43,970	0.55	0.33, 0.91
Current EPT use at baseline				
Used for <10 years	50	202,688	0.83	0.56, 1.22
Used for ≥10 years	23	50,645	0.89	0.55, 1.43

Abbreviations: CI, confidence interval; EPT, estrogen-plus-progestin therapy; ET, estrogen-only therapy; HR, hazard ratio; HT, hormone therapy.

[a] Analysis of duration of ET use was restricted to never users of HT (referent) and current ET users at baseline. Analysis of duration of EPT use was restricted to never users of HT (referent) and current EPT users at baseline.

[b] All models were stratified by age at baseline (in single years) and adjusted for race/ethnicity (non-Hispanic white, black, or other), body mass index, measured as weight in kilograms divided by height in meters squared (<25, 25 to <30, ≥30, or unknown), age at menarche (≤11, 12, 13, or ≥14 years or unknown), total number of full-term pregnancies (nulligravid, gravid nulliparous, 1–2 full-term pregnancies, ≥3 full-term pregnancies, or unknown), smoking status (never, former, current, or unknown), and history of diabetes (no or yes).

statistical power, or lack of information on HT formulation. CTS members have a high prevalence of HT use, and the CTS has information on the 2 main preparation types, that is, ET and EPT. None of the previous studies addressed the associations of ET use and EPT use separately (28–31, 34, 38, 45–47, 62). In the present study, no duration-response effect of ET use on pancreatic cancer risk was observed (Table 3), although the statistical power was limited for that analysis.

The apparent inverse association between ET use and pancreatic cancer risk is consistent with the inhibitory effect of estrogen on the growth of preneoplastic pancreatic lesions or transplanted pancreatic carcinoma in rats (19, 20). It might also result from the beneficial impact of hormone therapy on carbohydrate metabolism. Results from several large randomized clinical trials suggested that hormone therapy reduces the incidence of diabetes (63–65) and fasting glucose levels (63–66), which may be important in pancreatic cancer. In fact, a dose-response relationship between fasting serum glucose levels and pancreatic cancer risk has been reported (67). Yet, hormone regimens used in these trials have included both ET and EPT: conjugated equine estrogen (CEE) alone (63), CEE and medroxyprogesterone acetate (64–66), and CEE and micronized progesterone (66). One additional randomized clinical trial using 17-β estradiol suggested that addition of progestin (norethindrone) counteracted the effect of 17-β estradiol in reducing insulin levels (68). Further investigation into the specific and relative effects of exogenous estrogens and progestins on pancreatic cancer risk is needed.

Previous cohort studies reported overall null associations between OC use and pancreatic cancer risk (28–31). However, 2 of these studies noted a 20%–30% statistically nonsignificant increase in risk for OC use of longer than 3 or 5 years (30, 31). In the present study, a longer duration of OC use (≥10 years) compared with never use of OCs was associated with a 72% increased risk of pancreatic cancer. It is unclear why the associations of pancreatic cancer with OC use and with ET use are in opposite directions. Although these findings may reflect residual confounding due to incomplete control for characteristics of long-term OC users and ET users, it is notable that the association of estrogen with glucose metabolism varies by dosage and formulation of hormone components (69). The commonly used estrogens in OCs and ET are ethinyl estradiol (70) and CEE (71), respectively. Use of OCs that contain estrogen and progestin has been associated with increased insulin levels and unfavorable glucose tolerance (72), and this association was stronger for high-dose OCs and varied depending on the type of progestin (72, 73).

Consistent with our findings, most previous studies did not observe associations of reproductive and menstrual factors with pancreatic cancer risk. Age at menarche has not been associated with pancreatic cancer risk in prospective studies (27–31, 41, 42). For parity, cohort studies have reported positive (28, 42), inverse (30), and null associations (27, 29, 37, 41). For age at menopause, most prospective studies (27, 30, 31, 41) reported no association, with 2 studies reporting a positive (42) or inverse (29) association. Data have been limited and mixed on the role of breastfeeding: Two studies found no association (30, 41), whereas another reported lower risk among women who had breastfed (42).

The present study has several key strengths. First, the proportions of ever-smokers and current smokers at baseline in the CTS (roughly 30% and 5%, respectively) are substantially (4- to 12-fold) lower than the proportions in comparable cohort studies (28–31, 41). Smoking has been associated with pancreatic cancer, as well as with a number of the exposures of interest in previous studies, including parity (37, 42), age at first birth (37), lower serum estrogen (74), and earlier menopause (75, 76). Thus, the CTS allows for an analysis of reproductive factors with substantially less likelihood of uncontrolled confounding due to smoking. Additional strengths of our study include its prospective design and the collection of extensive hormone-related exposure information.

Although our study had a relatively large number of pancreatic cancer cases compared with many previously published studies that addressed similar exposures, some exposure categories had a limited number of cases. Additional limitations of the present analysis include the fact that exposure assessment was based on the baseline questionnaire and 1 follow-up

questionnaire (in 2000, for HT analysis). Thus, possible misclassification of certain exposure factors is of concern, most notably HT use after publication of the Women's Health Initiative results in 2002 (57). However, truncation of follow-up at June 30, 2002, did not materially alter the results from those presented. One concern might be that smoking status, which obtained at baseline, could be misclassified, and of particular concern would be if women initiated smoking during follow-up. Although we did not collect general information on smoking after baseline, in our recent follow-up questionnaire collected in 2005–2006, we did ask about smoking status before and during the first pregnancy for parous women. According to data from this follow-up questionnaire, there were 1,432 young (20–39 years of age at baseline) respondents who were never-smokers at baseline and who had their first pregnancy after baseline. Of these, 99.9% reported that they never smoked up until their first pregnancy, suggesting that the majority of young women who were never-smokers at baseline, at least those who became parous after baseline, did not initiate smoking after baseline. In addition, although we cannot rule out the uptake of smoking, the continuous decline in smoking prevalence in adult women in California during the period of 1996–2008 across all age groups, including women aged 18–24 years and 25–44 years, makes this unlikely (77). If any change in smoking status has occurred during follow-up, it would most likely be due to current smokers (less than 5% of the cohort) quitting (78). Our observation of similar or stronger results when restricting the analyses to never-smokers at baseline suggests that any residual confounding by misclassification of smoking status was minimal. The low prevalence of smoking in the CTS limits generalizability of our findings. In conclusion, these data suggest that ET use may decrease pancreatic cancer risk, whereas long-term OC use may increase pancreatic cancer risk.

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(Appendix follows)

Appendix Table 1. Hazard Ratios and 95% Confidence Intervals for the Association Between Pancreatic Cancer Risk and Duration of High-dose Oral Contraceptive Use in the California Teachers Study, 1995–2009

Duration and Timing of High-dose OC Use	No. of Cases	Person-years	Multivariable HR[a]	95% CI
Never used OCs	156	437,932	1	Referent
Stopped using OCs before 1974				
Used for <1 year	17	69,551	1.27	0.75, 2.13
Used for 1 to <5 years	32	174,803	1.08	0.71, 1.65
Used for 5 to <10 years	24	85,213	1.40	0.88, 2.22
Used for ≥10 years	9	14,745	2.08	1.05, 4.12
P for trend			0.026	
Started using OCs after 1975	4	225,928	0.86	0.25, 2.95

Abbreviations: CI, confidence interval; HR, hazard ratio; OC, oral contraceptive.

[a] All models were stratified by age at baseline (in single years) and adjusted for race/ethnicity (non-Hispanic white, black, or other), body mass index, measured as weight in kilograms divided by height in meters squared (<25, 25 to <30, ≥30, or unknown), menopausal status (premenopausal, postmenopausal, or unknown), hormone therapy use (never, estrogen-only therapy, estrogen-plus-progestin therapy, both estrogen-only therapy and estrogen-plus-progestin therapy, progestin-only therapy, or unknown), age at menarche (≤11, 12, 13, or ≥14 years or unknown), total number of full-term pregnancies (nulligravid, gravid nulliparous, 1–2 full-term pregnancies, ≥3 full-term pregnancies, or unknown), smoking status (never, former, current, or unknown), and history of diabetes (no or yes).